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(54) Imidazole compounds, their preparation and use.

(57) The application discloses benzimidazole derivatives, pharmaceutical preparations comprised the compounds, their preparation and use in the treatment of disorders of the Central Nervous System such as ischemia, migraine, epilepsia, psychosis, Parkinsonism and depression.

EP 0 520 200 A2

The present invention relates to therapeutical active compounds and their use as well as to pharmaceutical preparations comprising the compounds. The compounds of the invention possess valuable activity as calcium channel blockers which make them useful in the treatment of anoxia, ischemia, psychosis and migraine for example.

It is well known that an accumulation of calcium (calcium overload) in the brain is seen after anoxia, ischemia, migraine and other hyperactivity periods of the brain, such as after epileptic convulsions. An uncontrolled high concentration of calcium in the brain cells is known to cause most of the degenerative changes connected with above diseases. Therefore compounds which can block the calcium channels of brain cells will be useful in the treatment of anoxia, ischemia, migraine, epilepsia and in the prevention of the degenerative changes connected with the same.

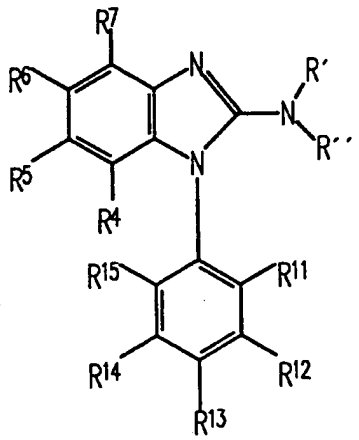
Compounds blocking the socalled L-type calcium channels in the central nervous system (CNS) will be useful for the treatment of the above disorders by directly blocking the calcium uptake in the CNS.

Further, it is well known that the socalled N-type of calcium channels are involved in the regulation of the neurotransmitter release. Compounds blocking the N-type of calcium channels will indirectly and very powerfully prevent calcium overload in CNS after the hyperactivity periods of the brain as described above by inhibiting the enhanced neurotransmitter release seen after such hyperactivity, and especially the neurotoxic enhanced glutamate release after such hyperactivity periods of the CNS. Furthermore, blockers of the N-type of calcium channels will dependent upon the selectivity of the compound in question inhibit the release of various other neurotransmitters such as aspartate, GABA, glycine, dopamine, serotonin and noradrenaline and therefore blockers of N-type of calcium channels may be useful in the treatment of psychosis, Parkinsonism, depression, epilepsia and other convulsive disorders.

It is an object of the present invention to provide compounds being able to block the L-type and/or the N-type calcium channels.

The invention then, inter alia, comprises the following, alone or in combination.

A method of treating a disorder of a mammal, including a human, which is responsive to the blockade of N-type and/or L-type of calcium channels, which comprises administering to a patient in need thereof a therapeutically effective amount of a compound having the formula:



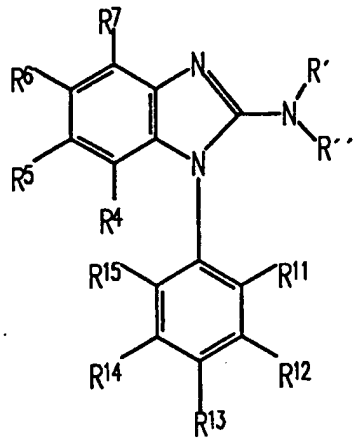
wherein

R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;

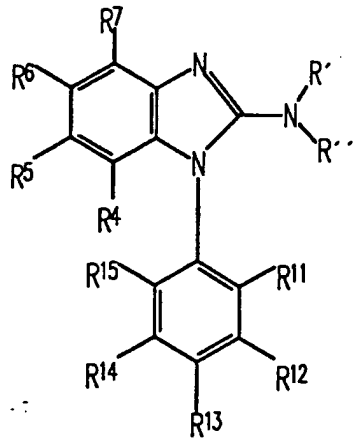
R^4, R^5, R^6, R^7 independently of each other are hydrogen, halogen, CF_3, or CN;

R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched; R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, phenyl, piperidyl, pyrrolidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof,

and the method as above wherein anoxia, ischemia, migraine, epilepsia, and the prevention of the degenerative changes connected with anoxia, ischemia, migraine, and epilepsia is treated,
and the method as above wherein psychosis, Parkinsonism, depression, epilepsia or other convulsive disorders are treated,
further a compound having the formula



wherein
R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;
R^4, R^5, R^6 and R^7 independently of each other are hydrogen, halogen, CF_3 or CN;
R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched;
two of R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{15} wherein R^{15} is C_{1-4}-alkyl which may be straight or branched, or phenyl and the last of R^{12}, R^{13} and R^{14} is pyrrolidyl, piperidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof,
and a compound as above which is 1-(2-hydroxy-5-phenyl-phenyl)-2-amino-benzimidazole,
and a compound as above which is 1-(2-methoxy-5-phenyl-phenyl)-2-amino-benzimidazole,
and a compound as above which is 1-(2-methoxy-5-phenyl-phenyl)-2-amino-5-trifluoromethyl-benzimidazole,
and a compound as above which is 1-(3-(1-piperidyl)-phenyl)-5-fluoro-2-amino-benzimidazole,
still further a pharmaceutical composition comprising as active ingredient an effective amount of a compound as first above,
further a method of preparing a compound having the formula



wherein

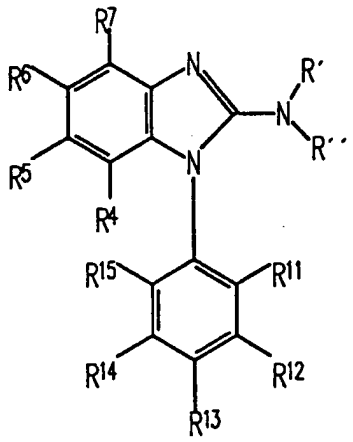
R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;

R^4, R^5, R^6 and R^7 independently of each other are hydrogen, halogen, CF_3 or CN;

R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched;

two of R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, or phenyl and the last of R^{12}, R^{13} and R^{14} is pyrrolidyl, piperidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof comprising:

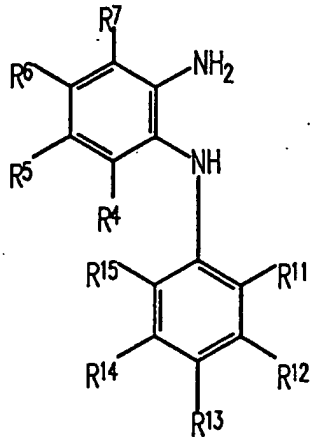
a) reacting a compound having the formula



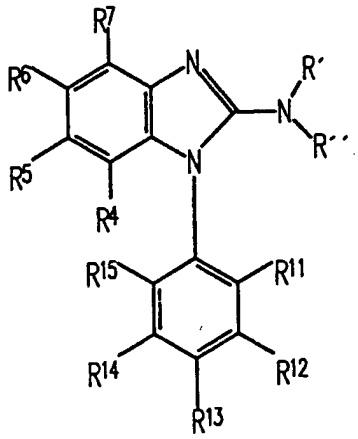
wherein

R', R'', R^4, R^5, R^6, R^7, and R^{15} have the meanings set forth above and wherein one of R^{12}, R^{13} and R^{14} is iodine and the other of R^{12}, R^{13} and R^{14} have the meanings set forth above, with R^{12}-$B(OH)_2$, R^{13}-$B(OH)_2$ or R^{14}-$B(OH)_2$, wherein R^{12}, R^{13} and R^{14} have the meanings set forth above, to form a compound of the invention, or

b) reacting a compound having the formula

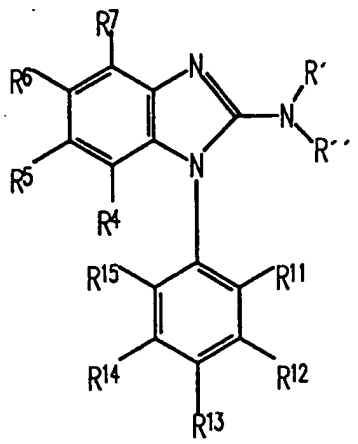


wherein
R^4, R^5, R^6, R^7, R^{11}, R^{12}, R^{13}, R^{14}, and R^{15} have the meanings set forth above, with cyanogen bromide, to form a compound of the invention,
and the method as above wherein 1-(2-hydroxy-5-phenyl-phenyl)-2-amino-benzimidazole is prepared,
and the method as above wherein 1-(2-methoxy-5-phenyl-phenyl)-2-amino-benzimidazole is prepared,
and the method as above wherein 1-(2-methoxy-5-phenyl-phenyl)-2-amino-5-trifluoromethyl-benzimidazole is prepared,
and the method as above wherein 1-(3-(1-piperidyl)-phenyl)-5-fluoro-2-amino-benzimidazole is prepared,
as well as the use of a compound having the formula

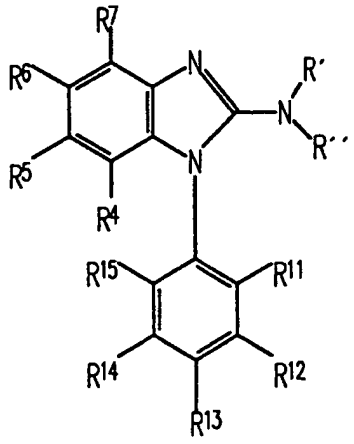


wherein
R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;
R^4, R^5, R^6, R^7 independently of each other are hydrogen, halogen, CF_3, or CN;
R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched;
R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, phenyl, piperidyl, pyrrolidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof for the preparation of a medicament

useful in the treatment of disorders of a mammal, including a human, responsive to the blockade of N-type and/or L-type of calcium channels,
and the use of a compound having the formula,



wherein
R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;
R^4, R^5, R^6, R^7 independently of each other are hydrogen, halogen, CF_3, or CN;
R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched;
R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, phenyl, piperidyl, pyrrolidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof for the preparation of a medicament useful in the treatment of anoxia, ischemia, migraine, epilepsia, psychosis, Parkinsonism depression, and the prevention of the degenerative changes connected with anoxia, ischemia, migraine and epilepsia,
and the use of a compound having the formula



wherein
R' and R''independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;

R^4, R^5, R^6 and R^7 independently of each other are hydrogen, halogen, CF_3 or CN;
R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched; two of R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, or phenyl and the last of R^{12}, R^{13} and R^{14} is pyrrolidyl, piperidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof for the preparation of a medicament useful in the treatment of disorders of a mammal, including a human, responsive to the blockade of N-type and/or L-type of calcium channels.

Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, oxalate and the acetate.

Biology

A high influx of calcium from extracelluar compartments into neurons is seen after opening of voltage operated calcium channels. Such opening of calcium channels may be induced by depolarization of neuronal membranes.

A crude synaptosome preparation contains small vesicles surrounded by neuronal membranes, and it is possible to study an opening of the voltage operated calcium channels in such a preparation.

In the below described test influx of ^{45}Ca into synaptosomes is studied under depolarized conditions. The effect of test substances on the depolarization induced calcium uptake can thus be studied.

Test Procedure

The cerebral cortex from a male Wistar rat is homogenized in 20 ml ice cold 0.32M saccharose. In the following steps the temperature is kept at 0 °C to 4 °C. The homogenate is centrifuged at 1,000 x g for 10 minutes and the supernatant recentrifuged for 20 minutes at 18,000 x g. The obtained pellet is resuspended in 0.32M saccharose (10 ml per g of original tissue).

Aliquots of 0.05 ml of the hereby obtained synaptosome suspension are added to glass tubes containing 0.625 ml of a NaCl buffer (136 mM Nacl, 4 Mm KCl, 0.35 mM $CaCl_2$, 1.2 mM $MgCl_2$, 20 mM Tris HCl, 12 mM glucose, pH 7.4) as well as 0.025 ml of different test substances in 48% ethanol. These tubes are pre-incubated for 30 minutes on ice and thereafter for 6 minutes at 37 °C.

^{45}Ca uptake is initiated by addition to above glass-tubes of 0.4 ml $^{45}CaCl_2$ (specific activity: 29-39 Ci/g; 0.5 Ci per tube). For depolarized samples the 0.4 ml $^{45}CaCl_2$ contain KCl (145 mM) and for non-depolarized NaCl (145 mM). The samples are incubated for 15 seconds.

The ^{45}Ca uptake is stopped by filtering through glass fibre filters, which are subsequently washed 3 times with an ice cold solution of 145 mM KCl, 7 mM EGTA and 20 mM Tris HCl, pH 7.4 (5.0 ml). The radioactivity on the filters are measured by liquid scintillation spectrometry. Experiments are performed in duplicate.

Sample preparation

Above test substances are dissolved in for example 10 ml 48% ethanol at a concentration of 0.44 mg/ml. Dilutions are made in ethanol. Test substances are tested at concentrations of 0.1, 0.3, 1, 3, 10 .... µg/ml.

Results

The test value is given as IC_{50}, that is the concentration in µM of the test substances, which inhibit 50% of the potassium stimulated uptake of ^{45}Ca. The uptake in potassium depolarized samples are corrected for basal uptake in non-depolarized samples. The IC_{50} value is determined from a dose response curve.

The results obtained by testing selected compounds according to the invention are presented in below table

Table

Compound	IC_{50} (μM)
2-(2,5-dimethoxyphenyl)-2-amino-5-trifluoromethyl-benzimidazole	0.7
1-(2-hydroxy-5-chlorophenyl)-5-trifluoromethyl-2-amino-benzimidazole	2.0
1-(5-(1-pyrrolidinyl)-phenyl)-2-amino-5-fluoro-benzimidazole	2.0

It has been found (electrophysiological studies using the patch-clamp technique as described by Hamill et al., Pflügers Arch. 391, 85-100 (1981)), that the compounds of the invention block the N-type of calcium channels. Several compounds block the N-type calcium channels in these studies at concentrations from 0.5-10 μM. Examples of such compounds are 1-(2-hydroxy-5-phenyl-phenyl)-2-amino-5-trifluoromethyl-benzimidazole, and 1-(2-methoxy-5-phenyl-phenyl)-2-amino-5-trifluoromethyl-benzimidazole. Therefore the compounds are useful in the treatment of anoxia, ischemia and migraine (see also WO 91/07980).

Further it has been found that the compounds of the invention, for example 1-(2-hydroxy-5-phenyl-phenyl)-2-amino-benzimidazole potently antagonize hypermotility in mice as induced by amphetamine or cocaine. This is in full accordance with the influence of N-type calcium channel blockers on transmitter release in the central nervous system. Therefore the compounds of the invention are useful as anti-psychotics.

Pharmaceutical Compositions

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredient or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

Method of Treating

Due to the high degree of activity the compounds of the invention may be administered to a subject, e.g., a living animal body, in need of alleviation, treatment, or amelioration of an indication which is sensitive to the activity or influence of the compounds of the present invention including sensitive to the Ca channel blocking properties of the compounds of the invention. The compounds of the invention are preferably administered in the form of an acid addition salt thereof, concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether oral, rectal, or parenteral (including subcutaneous) route, in an effective amount. Suitable dosage ranges are 0.1-500 milligrams daily, preferably 1-100 milligrams daily, and especially 1-30 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preferences and experience of the physician or veterinarian in charge.

The following examples will illustrate the invention further, however they are not to be construed as limiting.

Example 1.

1-(2-Hydroxy-5-trifluoromethylphenyl)-2-amino-5-trifluoromethyl benzimidazole (1P). To a solution of **2P** (4.17 g, 11.2 mmol) in a mixture of DMF and triethylamine was added cyanogen bromide (1.54 g, 14.6 mmol). The mixture was stirred for 26 h at room temperature and then diluted with water (150 ml), filtered, and neutralized with 2M aqueous sodium hydroxide. The product was filtered off and recrystallized from ethanol. Yield 430 mg, mp >360 °C.

In addition to compounds **1A-1AG** also **1-[1-(2-hydroxynaphtyl)]-2-aminobenzimidazole** (mp 210 °C)

was prepared according to example 1. The starting material in the former case was N-(2-aminophenyl)-1-amino-2-naphthol.

Example 2.

1-(2-hydroxy-5-phenyl-phenyl)-2-aminobenzimidazole (1AC). To a solution of **1H** (100 mg, 0.32 mmol) in dry methylene chloride under nitrogen, was added BBr_3 (0.036 ml, 0.38 mmol). The mixture was stirred at room temperature for 2 h. Water was then added and the pH was adjusted to 7 by the addition of an aqueous solution of sodium carbonate. Extraction with methylene chloride and drying over $MgSO_4$ was followed by column chromatography on silica gel with methylene chloride/ethanol (25:1) as eluent. Yield: 40 mg, 0.13 mmol, mp 259-261 °C.

Example 3.

2-Amino-4,5'-dichloro-2'-hydroxydiphenylamine (20). A solution of **30** (6.41 g, 21.5 mmol) in a mixture of THF (100 ml) and ethanol (200 ml) was hydrogenated over 5% palladium on charcoal (500 mg) at ambient pressure until the uptake of hydrogen ceased. The mixture was filtered through celite into a flask containing 2.5 ml conc. HCl. Evaporation to dryness gave the product as a dark solid.
Yield: 6.47 g, mp 250-280 °C (dec.).

In addition to compounds **2A-2Z** also **N-(2-aminophenyl)-1-amino-2-naphthol** (mp 239-246 °C) was prepared according to exam-ple 3. The starting material in the former case was N-(2-nitrophenyl)-1-amino-2-naphthol.

Example 4.

2,5-Dimethoxy-2'-nitro-4'-trifluoromethyldiphenylamine (3N). To a solution of 2,5-dimethoxy aniline (20 g, 130 mmol) in dry DMF under nitrogen, was added 80% NaH in mineral oil (4.31 g, 143 mmol). The mixture was stirred at room temperature for 1 h and then 4-chloro-3-nitrobenzotrifluoride (29.45 g, 130 mmol) was added. After stirring overnight at room temperature the excess sodium hydride was destroyed by the addition of a small amount of water. Dilution with 0.3 M aqueous HCl gave a crystalline product which was filtered off and washed, first with water and then with petroleum ether. The product was dissolved in methylene chloride and filtered through a short column of silica gel. After evaporation of the solvent an orange coloured crystalline solid remained. Yield 15.33 g, mp 93-95 °C.

In addition to compounds **3A-3Z** also **N-(2-nitrophenyl)-1-amino-2-naphthol** (mp 185-188 °C) was prepared according to example 3. The starting material in the former case was 3-(2-nitrophenyl)benzo[e]-benzoxazole-2-one.

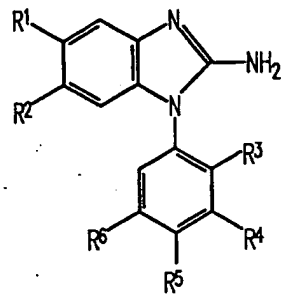
Example 5.

4,5'-Bistrifluoromethyl-2'-hydroxy-2-nitrodiphenylamine (3P). To a solution of **4E** (5.0 g, 12.75 mmol) in dimethoxy ethane was added 38.25 ml 1M aqueous NaOH. The mixture was stirred overnight. Dilution with water and neutralization with 1M HCl was followed by extraction with ether. Evaporation at room temperature gave an orange coloured oil that crystallized upon storage in the freezer.
Yield: 4.01 g, mp 120-123 °C.

Example 6.

1-(2-Methoxy-5-chlorophenyl)-2-dimethylamino-5-trifluoromethylbenzimidazole. To a solution of 1Q (o.5 g, 1.37 mmol) in ethanol was added K_2CO_3 (0.38 g, 2.74 mmol) and iodometane (1.94 g, 13.7 mmol). The mixture was refluxed for 20 h, filtered, and evaporated to dryness. The product was purified by chromatography on silica gel with methylene chloride/methanol (9:1) as eluent. Yield 50 mg, mp 230-234 °C.

Table 1.



No	R1	R2	R3	R4	R5	R6	Mp/°C	Starting Material
1A	H	H	OCH_3	H	H	Cl	207–208	2A
1B	CF_3	H	OH	H	H	H	190–195	2B
1C	CF_3	H	OCH_3	H	H	Ph	227–231	2C
1D	Cl	Cl	OCH_3	H	H	Cl	222–224	2D
1E	CF_3	H	H	CF_3	H	H	174–175	2E

1F	CF_3	H	H	OCH_3	H	CF_3	194–195	2F
1G	CN	H	OH	H	H	Cl	250–254	2G
1H	H	H	OCH_3	H	H	Ph	234–238	2H
1I	CF_3	H	OCH_3	H	H	CF_3	214–217	2I
1J	CF_3	H	H	Cl	H	H	221–224	2J
1K	CF_3	H	OCH_3	H	H	CH_3	210–212	2K
1L	H	H	OH	H	H	Cl	276–278	2L
1M	CF_3	H	OCH_3	H	H	F	180–184	2M
1N	CF_3	H	OCH_3	H	H	OCH_3	192–194	2N
1O	Cl	H	OH	H	H	Cl	286–288	2O
1P	CF_3	H	OH	H	H	CF_3	>360	2P
1Q	CF_3	H	OH	H	H	Cl	292–293	2Q
1R	CF_3	H	H	H	CF_3	H	220–222	2R
1S	CF_3	H	CF_3	H	H	H	201–204	2S

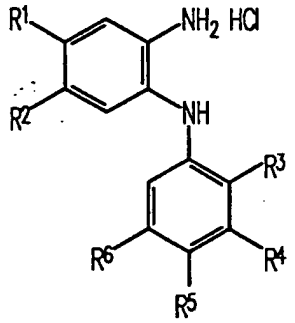
1T	CF_3	H	H	Cl	Cl	Cl	208–210	2T
1U	CF_3	H	H	CF_3	Cl	H	213–215	2U
1V	CF_3	H	H	I	H	H	190–193	2V
1W	CF_3	H	H	1-pyr.	H	H	239–241	2W
1X	CF_3	H	H	H	OPh	H	58–63	2X
1Y	F	H	H	1-pip.	H	H	151–153	2Y
1Z	CF_3	H	H	OPh	H	H	177–179	2Z
1AA	Cl	Cl	OH	H	H	Cl	>360	1D
1AB	CF_3	H	H	H	H	CH_3	202–206	1F
1AC	H	H	OH	H	H	Ph	259–261	1H
1AD	CF_3	H	OH	H	H	CH_3	278–281	1K
1AF	CF_3	H	OH	H	H	F	230–232	1M
1AG	CF_3	H	OH	H	H	OH	149–151	1N

1-pyr. =1-pyrrolidino.

1-pip. = 1-piperidino.

Compounds 1A-1Z were prepared according to example 1 and compounds 1AA-1AG according to example 2.

Table 2.



No	R^1	R^2	R^3	R^4	R^5	R^6	mp/°C	Starting material
2A	H	H	OCH_3	H	H	Cl	156–168 (d)	3A
2B	CF_3	H	OH	H	H	H	200–220 (d)	3B
2C	CF_3	H	OCH_3	H	H	Ph	181–184	3C
2D	Cl	Cl	OCH_3	H	H	Cl	174–176	3D
2E	CF_3	H	H	CF_3	H	H	184–186	3E

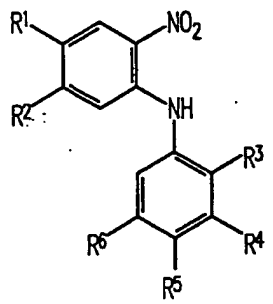
2F	CF_3	H	H	OCH_3	H	CF_3	167–169	3F
2G	CN	H	OH	H	H	Cl	170–172	3G
2H	H	H	OCH_3	H	H	Ph	127–150 (d)	3H
2I	CF_3	H	OCH_3	H	H	CF_3	177–180	3I
2J	CF_3	H	H	Cl	H	H	182–184	3J
2K	CF_3	H	OCH_3	H	H	CH_3	148–151	3K
2L	H	H	OH	H	H	Cl	245 (d)	3L
2M	CF_3	H	OCH_3	H	H	F	182–184	3M
2N	CF_3	H	OCH_3	H	H	OCH_3	156–160	3N
2O	Cl	H	OH	H	H	Cl	250–280	3O
2P	CF_3	H	OH	H	H	CF_3	200–205	3P
2Q	CF_3	H	OH	H	H	Cl	202–207	3Q
2R	CF_3	H	H	H	CF_3	H	163–165	3R
2S	CF_3	H	CF_3	H	H	H	78–80	3S
2T	CF_3	H	H	Cl	Cl	Cl	216–218	3T
2U	CF_3	H	H	CF_3	Cl	H	184–186	3U
2V	CF_3	H	H	I	H	H	182–185	3V
2W	CF_3	H	H	1-pyr.	H	H	210 (d)	3W
2X	CF_3	H	H	H	OPh	H	*	3X
2Y	F	H	H	1-pip.	H	H	220 (d)	3Y
2Z	CF_3	H	H	OPh	H	H	180–183	3Z

1-pyr.=1-pyrrolidyl.

1-pip.=1-piperidyl.

*= Isolated in an impure state unsuitable for melting point determination.

Table 3.



No	R^1	R^2	R^3	R^4	R^5	R^6	mp/°C	Starting material
3A	H	H	OCH_3	H	H	Cl	112–113	c
3B	CF_3	H	OH	H	H	H	*	4A
3C	CF_3	H	OCH_3	H	H	Ph	*	c
3D	Cl	Cl	OCH_3	H	H	Cl	*	c
3E	CF_3	H	H	CF_3	H	H	80–82	c
3F	CF_3	H	H	OCH_3	H	CF_3	94–96	c

3G	CN	H	OH	H	H	Cl	210–212	4B
3H	H	H	OCH_3	H	H	Ph	oil	c
3I	CF_3	H	OCH_3	H	H	CF_3	86–88	c
3J	CF_3	H	H	Cl	H	H	92–94	c
3K	CF_3	H	OCH_3	H	H	CH_3	106–109	c
3L	H	H	OH	H	H	Cl	156–158	4C
3M	CF_3	H	OCH_3	H	H	F	131–134	c
3N	CF_3	H	OCH_3	H	H	OCH_3	93–95	c
3O	Cl	H	OH	H	H	Cl	199–203	4D
3P	CF_3	H	OH	H	H	CF_3	120–123	4E
3Q	CF_3	H	OH	H	H	Cl	179–181	4F
3R	CF_3	H	H	H	CF_3	H	67–69	c
3S	CF_3	H	CF_3	H	H	H	87–89	c
3T	CF_3	H	H	Cl	Cl	Cl	137–140	c
3U	CF_3	H	H	CF_3	Cl	H	93–94	c
3V	CF_3	H	H	I	H	H	98–101	c
3W	CF_3	H	H	1-pyr.	H	H	oil	c
3X	CF_3	H	H	H	OPh	H	94–96	c
3Y	F	H	H	1-pip.	H	H	oil	c
3Z	CF_3	H	H	OPh	H	H	oil	c

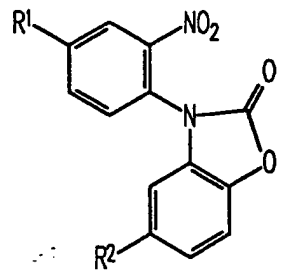
1-pyr.=1-pyrrolidyl.

1-pip.=1-piperidyl.

*=Isolated in an impure state unsuitable for melting point determination.

c=Prepared from commercially availabe or known anilines and 2-halo-1-nitrobenzenes.

Table 4.

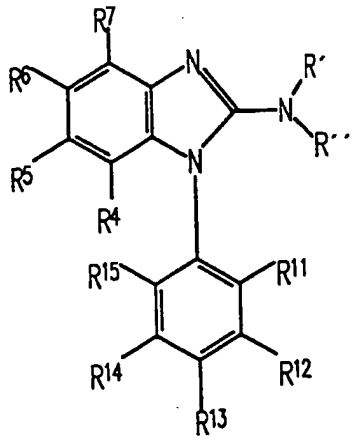


No.	R^1	R^2	mp/°C
4A	CF3	H	*
4B	CN	Cl	228–230
4C	H	Cl	121–123
4D	Cl	Cl	172–174
4E	CF3	CF3	154–156
4F	CF3	Cl	177–180

*=Isolated in an impure state unsuitable for melting point determination.

Claims

1. The use of a compound having the formula



wherein

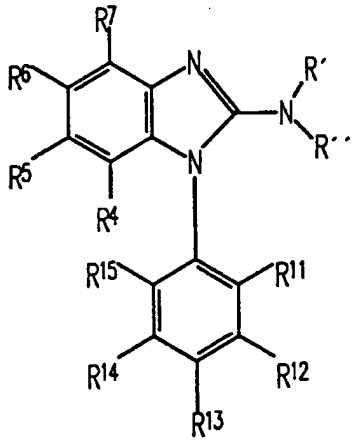
R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;

R^4, R^5, R^6, R^7 independently of each other are hydrogen, halogen, CF_3, or CN;

R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched;

R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, phenyl, piperidyl, pyrrolidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof for the preparation of a medicament useful in the treatment of disorders of a mammal, including a human, responsive to the blockade of N-type and/or L-type of calcium channels.

2. The use of a compound having the formula

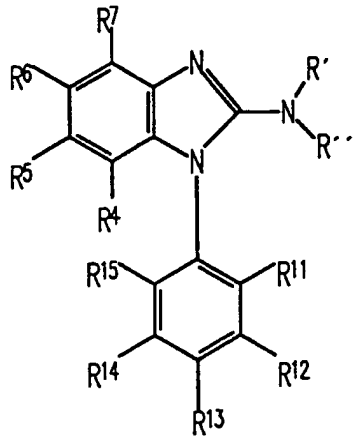


wherein

R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;

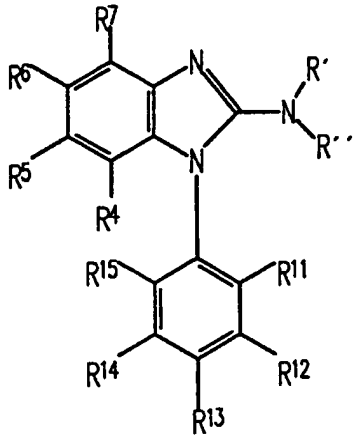
R^4, R^5, R^6, R^7 independently of each other are hydrogen, halogen, CF_3, or CN;
R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched;
R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, phenyl, piperidyl, pyrrolidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof for the preparation of a medicament useful in the treatment of anoxia, ischemia, migraine, epilepsia, psychosis, Parkinsonism depression, and the prevention of the degenerative changes connected with anoxia, ischemia, migraine and epilepsia.

3. The use of a compound having the formula



wherein
R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;
R^4, R^5, R^6 and R^7 independently of each other are hydrogen, halogen, CF_3 or CN;
R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched;
two of R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, or phenyl and the last of R^{12}, R^{13} and R^{14} is pyrrolidyl, piperidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof for the preparation of a medicament useful in the treatment of disorders of a mammal, including a human, responsive to the blockade of N-type and/or L-type of calcium channels.

4. A compound having the formula



wherein

R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;

R^4, R^5, R^6 and R^7 independently of each other are hydrogen, halogen, CF_3 or CN;

R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched;

two of R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, or phenyl and the last of R^{12}, R^{13} and R^{14} is pyrrolidyl, piperidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof.

5. A compound of claim 4 which is 1-(2-hydroxy-5-phenyl-phenyl)-2-amino-benzimidazole.

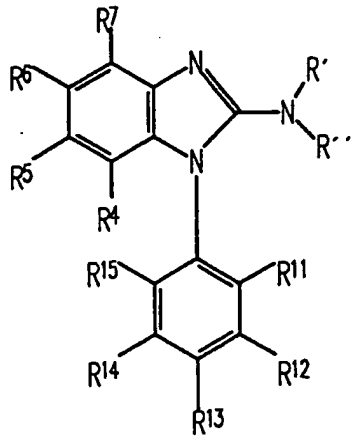
6. A compound of claim 4 which is 1-(2-methoxy-5-phenyl-phenyl)-2-amino-benzimidazole.

7. A compound of claim 4 which is 1-(2-methoxy-5-phenyl-phenyl)-2-amino-5-trifluoromethyl-benzimidazole.

8. A compound of claim 4 which is 1-(3-(1-piperidyl)-phenyl)-5-fluoro-2-amino-benzimidazole.

9. A pharmaceutical composition comprising as active ingredient an effective amount of a compound of claim 4.

10. A method of preparing a compound having the formula



wherein

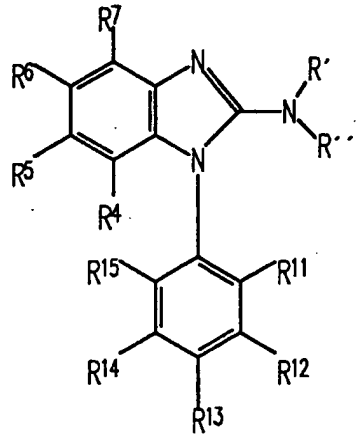
R' and R'' independently are hydrogen or C_{1-4}-alkyl which may be straight or branched, or R' and R'' together form an alkylene chain of 2-6 carbon atoms;

R^4, R^5, R^6 and R^7 independently of each other are hydrogen, halogen, CF_3 or CN;

R^{11} is hydrogen, halogen, CF_3, hydroxy or OR^I wherein R^I is C_{1-4}-alkyl which may be straight or branched;

two of R^{12}, R^{13} and R^{14} independently are hydrogen, halogen, CF_3, C_{1-4}-alkyl which may be straight or branched, OH, OR^{16} wherein R^{16} is C_{1-4}-alkyl which may be straight or branched, or phenyl and the last of R^{12}, R^{13} and R^{14} is pyrrolidyl, piperidyl, or phenyl which may be substituted one or more times with halogen, CF_3, CN, C_{1-4}-alkyl which may be straight or branched, OH, NO_2, CO_2H, NH_2, OR^{II} wherein R^{II} is C_{1-4}-alkyl which may be straight or branched, CO_2R^{III} wherein R^{III} is C_{1-4}-alkyl which may be straight or branched, $NR^{IV}R^V$ wherein R^{IV} and R^V independently are hydrogen, C_{1-6}-alkyl which may be straight or branched, acyl, or wherein R^{IV} and R^V together form an alkylene chain of 2-6 carbon atoms; R^{15} is hydrogen or together with R^{14} form an extra benzo ring; or a pharmaceutically acceptable addition salt thereof comprising:

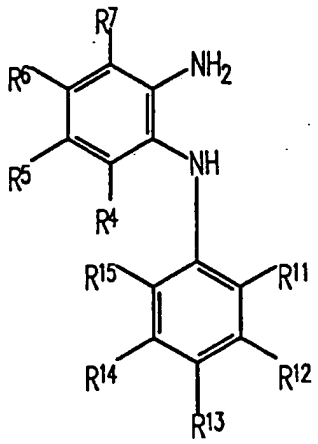
a) reacting a compound having the formula



wherein

R', R'', R^4, R^5, R^6, R^7, and R^{15} have the meanings set forth above and wherein one of R^{12}, R^{13} and R^{14} is iodine and the other of R^{12}, R^{13} and R^{14} have the meanings set forth above, with R^{12}-$B(OH)_2$, R^{13}-$B(OH)_2$ or R^{14}-$B(OH)_2$, wherein R^{12}, R^{13} and R^{14} have the meanings set forth above, to form a compound of the invention, or

b) reacting a compound having the formula



wherein
R^4, R^5, R^6, R^7, R^{11}, R^{12}, R^{13}, R^{14}, and R^{15} have the meanings set forth above, with cyanogen bromide, to form a compound of the invention.

11. The method of claim 10 wherein 1-(2-hydroxy-5-phenyl-phenyl)-2-amino-benzimidazole is prepared.

12. The method of claim 10 wherein 1-(2-methoxy-5-phenyl-phenyl)-2-amino-benzimidazole is prepared.

13. The method of claim 10 wherein 1-(2-methoxy-5-phenyl-phenyl)-2-amino-5-trifluoromethyl-benzimidazole is prepared.

14. The method of claim 10 wherein 1-(3-(1-piperidyl)-phenyl)-5-fluoro-2-amino-benzimidazole is prepared.